

Cost-consequence model comparing eltrombopag and romiplostim in pediatric patients with chronic immune thrombocytopenia

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Background: Immune thrombocytopenia (ITP) is an auto-immune disorder characterized by enhanced platelet destruction and, subsequently, the potential for increased bleeding. Thrombopoietin receptor (TPO-R) agonists have recently emerged as promising therapies for ITP patients who are refractory to other treatments. While eltrombopag (EPAG) is the only TPO-R agonist US Food and Drug Administration approved for use in pediatric patients, romiplostim (ROMI) has been used in Phase III clinical studies.

Methods: A cost-consequence model (CCM) was developed to evaluate the costs of EPAG, ROMI, and watch-and-rescue (W&R) in relation to their respective treatment outcomes in previously-treated pediatric chronic ITP (cITP) over a 26-week time horizon. The costs of drugs, administration, routine care, rescue medications, adverse events, and mortality were included. Data on platelet count response rate, bleeding events, and adverse events were derived from all relevant identified Phase III-registered clinical trials, health outcomes were compared via indirect treatment comparison.

Results: The overall estimated cost of EPAG per patient was US\$66,550, compared to US\$101,056 for ROMI and US\$32,720 for W&R. EPAG's lower cost compared to ROMI was largely due to lower drug costs (US\$62,202 vs US\$84,396), administration costs (US\$0 vs US\$1,955), and significantly lower costs due to severe bleeding (US\$354 vs US\$10,191). When assessing cost per severe bleeding event avoided, EPAG was dominant over ROMI (less expensive and more effective). EPAG was again dominant over ROMI when assessing the cost per responder and per bleeding event (any grade). Sensitivity analysis was consistent with the base case findings.

Conclusion: EPAG was the preferred TPO-R agonist to treat cITP when indirectly compared to ROMI, largely driven by its favorable severe bleeding outcomes and lower drug and administration costs.

Keywords: chronic immune thrombocytopenia, eltrombopag, romiplostim, cost-consequence, USA

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder in which platelets are disproportionately destroyed, resulting in a potential risk of increased bleeding. In children, ITP is a common cause of platelet deficiencies and when platelet counts drop below $10\text{--}20 \times 10^9/\text{L}$, clinically significant bleeding may occur.^{1,2} Approximately 40% of all patients diagnosed with ITP are children younger than 10 years.³ In most of these children, approximately 70%, ITP is a self-limiting disease that resolves naturally within 6 months.^{2,4,5} The disease becomes chronic in 20%–30% of pediatric patients, for whom

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spontaneous remission is unlikely.^{2,6} In the United States, the average estimate of the incidence of chronic ITP (cITP) is 5 children per 100,000 per year.⁷ Few children are affected by cITP but it may limit their activities and those who do not respond sufficiently to conventional therapies may be at risk for potentially life-threatening bleeding complications.^{2,5}

Individuals with cITP face an increased risk of bleeding due to their diminished platelet counts. Bleeding episodes commonly manifest as minor symptoms such as bruising, nosebleeds, and petechiae.² Additionally, cITP may be detrimental to quality of life, some patients experience depression and a fear of bleeding that limits routine activities.^{8,9} In rare cases, cITP is also associated with serious complications that include internal bleeding and major external bleeding. Intracranial bleeding is the most serious complication of ITP: although infrequent, it is considered to be life-threatening.³

To help prevent bleeding episodes, ITP therapies increase platelet counts. Many first-line therapies curb immune system-mediated platelet destruction. Thrombopoietin receptor (TPO-R) agonists, such as eltrombopag (EPAG) and romiplostim (ROMI), stimulate platelet production.¹⁰ These emerging therapies may provide a solution for patients whose first-line treatment with immunoglobulins, corticosteroids, or splenectomy proves ineffective.⁵

The efficacy of EPAG in pediatric patients was demonstrated in the randomized, double-blind, multi-center, Phase II and III trials PETIT and PETIT-2. In these trials, patients treated with EPAG had significantly higher platelet response rates (PETIT) and sustained platelet response rates (PETIT-2)

than placebo-treated patients.^{11,12} Orally-administered EPAG was well-tolerated and successful in maintaining platelet counts during longer-term therapy. This evidence supported US Food and Drug Administration (FDA) approval of EPAG for pediatric patients who are refractory or who had an inadequate response to first-line therapies. ROMI was similarly evaluated in a Phase III study of pediatric patients and high rates of platelet response were reported; however, its US approval is pending.

To date, no head-to-head trials have compared EPAG and ROMI and few indirect treatment comparisons have assessed their relative efficacy and safety.¹³ Several studies have assessed the cost of ROMI per patient who responded to treatment.^{14–16} However, these studies did not consider pediatric patients in a US setting and costs were not compared to the costs for EPAG treatment. One study compared EPAG and ROMI to “watch-and-rescue” (W&R) in a cost per response analysis: the TPO-R agonists proved cost-effective.¹⁷

Additional studies are required to better understand the role of TPO-R agonists in cITP treatment strategies. We present the results of a cost-consequences model (CCM) comparing EPAG to ROMI and W&R in previously-treated pediatric cITP patients in the US.

Materials and methods

Model perspective, patient populations and horizon/discounting

The model was constructed from a general US payer’s perspective and incorporated a time horizon of 26 weeks.

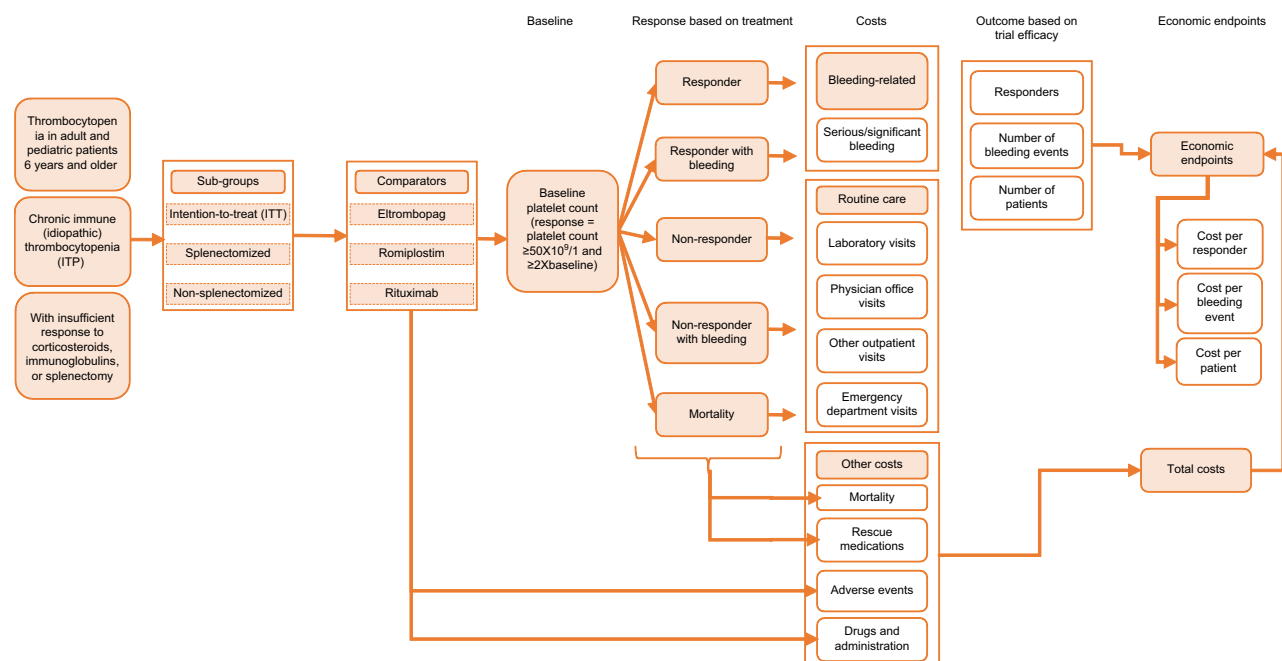


Figure 1 Model structure.

The population consisted of pediatric patients (1–17 years) with cITP who responded insufficiently to corticosteroids, immunoglobulins, and/or splenectomy. The trial period of ROMI (26 weeks) was incorporated as the time horizon because certain model endpoints are bound to within-trial data. As such, evidence from the published literature could be incorporated without relying on extrapolation techniques and additional assumptions. The model horizon was less than 1 year so no discounting was applied. A diagram of the model is presented in Figure 1.

Comparators

EPAG, ROMI, and W&R were selected as comparators following a targeted literature review. W&R treatment was based on the respective trials' placebo groups, as these patients would receive rescue therapy as needed. Rituximab and splenectomy, while common treatment options for cITP, were not included as comparators due to lack of comparability of the available subjects recruited to the trials. The two identified randomized trials assessing rituximab,^{17,18} which were pooled, only included adult cITP patients who were treated in the first line, differing from the EPAG and ROMI trials, which only included pediatric patients treated in the second line or greater. Furthermore, the rituximab trials only included non-splenectomized patients, which further limited the comparability among these trials and those used for EPAG and ROMI. Splenectomy was not included as a comparator due to the absence of any randomized clinical trials and because the population of the only identified retrospective study¹⁹ was not comparable to those used in the other treatments.

Indirect treatment comparison

The EPAG (PETIT2) clinical trial followed 63 EPAG-treated patients and 29 placebo-treated patients. The ROMI trial followed 42 ROMI-treated patients and 20 placebo-treated patients. By design, the two studies compared had similar baseline characteristics.^{11,20} The most notable differences at baseline were in the proportion of patients' ethnic origins (32% "East Asian" in the EPAG trial vs 7% "Asian" in the ROMI trial), the amount of time since diagnosis (3.4 years in the EPAG trial vs 1.9 years in the ROMI trial) and the proportion of male patients (52% in the EPAG trial vs 43% in the ROMI trial). Overall, the two trials were considered comparable enough to be entered into an indirect treatment comparison (ITC).

The ITC technique and results were identical to those reported in the Evidence Review Group (ERG) report, where ROMI efficacy data were adjusted to match the EPAG trial.

Therefore, EPAG and W&R (no drug treatment) efficacy data were taken directly from the trial.²¹ Frequentist ITC was employed and 95% confidence intervals were calculated. ROMI results were pooled using random effects models (Mantel-Haenszel method), which generated odds ratios for ROMI vs placebo. Odds ratios for EPAG were obtained from the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal.²² Odds ratios were estimated for splenectomized and non-splenectomized patients. Classical frequentist ITC was implemented using the Bucher (1997) method and 95% confidence intervals.²³

An additional endpoint was included to provide a more complete comparative effectiveness profile. In the ITC, bleeding events were the primary endpoint and platelet response was also considered.

Efficacy measures

A summary of the efficacy values and the resulting odds ratios for all clinical trials used in this analysis are presented in the Supplementary material.^{11,20} The raw values presented for ROMI were not used in the model and were instead matched to EPAG trial data for ITC, as described above. Therefore, W&R and EPAG results are untouched in the model, while the efficacy results for ROMI are adjusted.

Severe bleeding (WHO grades 3–5) was the primary measurement of efficacy in this analysis. The WHO bleeding scale is the most common measurement applied to quantify thrombocytopenia, and its validity is accepted. Mortality rates were derived as the product of treatment-specific severe bleeding rates, mortality of standard discharge in the US (2.39%) and relative mortality ratio for ITP (1.50).^{24,25} Moderate bleeding and platelet response were also assessed as secondary efficacy endpoints in our analysis. Cost-effectiveness was calculated using the severe bleeding, all bleeding, and platelet response endpoints.

Costs

The total cost of each treatment included the costs of drugs, administration, bleeding events, routine care, rescue medications, adverse events (all grades, affecting >20% of patients in at least one of the included trials), and mortality. The proportion of patients associated with these costs in each treatment arm was derived from clinical trial data if available, or from other published literature (Table 2).^{26,27}

All costs are listed in USD. All cost data were derived from US-based sources (no currency conversions were required) and US healthcare inflation (3.6%) was applied where no up-to-date data were available.²⁸

The available pack sizes of drugs may not provide the exact doses of drug required. Wastage was applied to dose calculations based on the received doses (ie, doses were rounded up to the nearest pack/vial size when necessary). Wastage and dose reduction accommodations were only applied for the primary therapies (EPAG and ROMI). It should be noted that ROMI is not yet FDA approved in pediatric patients and as such, the final costs are uncertain.

Costs incorporated in the analysis and their sources are summarized in Table 1.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were used to address uncertainty in the analysis. To perform these analyses, probabilistic distributions were directly applied to the base case model. The variations used in the PSA are presented in Table 2.

Results

Table 3 presents the overall costs and efficacy results for each primary therapy. Indirect treatment comparison efficacy data were used in the model (Table 3), while raw data are presented in the Supplementary material.

EPAG, ROMI, and W&R had total estimated costs of US\$66,550, US\$101,056, and US\$32,720, respectively. In this population, EPAG was estimated to cost US\$34,506 less

than ROMI. Compared with W&R, EPAG cost US\$33,830 more, while ROMI cost US\$68,336 more. Drug costs comprised the largest share of the cost for all comparators.

Severe bleeding (WHO grade 3–5) was assessed as the primary endpoint. EPAG demonstrated a 22.1% incremental benefit over ROMI and a 9.6% benefit over W&R, while ROMI showed an incremental benefit of 12.5% over W&R. Moderate bleeding (WHO grade 2) was also assessed, EPAG demonstrated a 15.7% and 8.3% incremental benefit over ROMI and W&R, respectively.

Table 2 Probabilistic sensitivity analysis parameters (intent-to-treat population)

Parameter	Point estimate	SE
Efficacy		
Overall response – EPAG	0.746	5.48%
Overall response – ROMI	0.714	6.97%
Severe bleeding (WHO 3–5) – EPAG	0.008	1.12%
Severe bleeding (WHO 3–5) – ROMI	0.119	5.00%
Use of rescue medication – EPAG	0.180	4.84%
Use of rescue medication – ROMI	0.405	7.57%
Costs		
Drug costs, administration costs, routine care costs, cost of bleeding (severe and moderate), adverse events costs, mortality costs	Variable point estimate	Standard error assumed at 20%

Abbreviations: EPAG, eltrombopag; ROMI, romiplostim.

Table 1 Costs incorporated and resources used

Resource	Unit Cost (inflation-adjusted)	Source
Comparators - Eltrombopag - Romiplostim	US\$10,253.00 (per pack) US\$6,492.00 (per pack)	AnalySource ²⁹ AnalySource ²⁹
Routine medical costs - Laboratory visits - Office Visits - Other outpatient visits - Emergency department visits	US\$27.00 (per visit) US\$78.00 (per visit) US\$367.00 (per visit) US\$260.00 (per visit)	Saleh, Fisher ³⁰
Rescue treatments - Blood transfusion - IVlg - IV methylprednisolone	US\$424.90 (per transfusion) US\$37.89 (per “pack”) US\$3.73 (per “pack”)	Utilization Lee, Thornton ³¹ Costs Blood transfusions ³² ; IV Ig and IV methylprednisolone ³³
Bleeding costs (with and without hospitalization)	US\$2,196.00 (without hospitalization) US\$44,590.00 (with hospitalization)	Lin ³⁴
Mortality costs	US\$55,238.00 (for ITP)	Centers for Medicare & Medicaid Services ³⁵
Administration costs - Subcutaneous injection - IV - Oral	US\$75.19 (per use) US\$136.41 (per use) US\$0.00 (per use)	CPT code 96413 (Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug); 96401 (chemotherapy administration, subcutaneous or intramuscular, non-hormonal anti-neoplastic)
Adverse Events	(See Supplementary Material for specific prevalence and costs)	Prevalence ^{26,27} ; Costs ²⁵

Note: All costs are listed in USD.

Abbreviations: IV, intravenous; IV Ig, intravenous immunoglobulin.

Table 3 Efficacy and costs

	EPAG	ROMI (naïve trial data)	ROMI (ITC data used in model)	Watch-and-rescue (W&R)	Adjusted ITC OR (EPAG/ROMI) (95% CI)	Δ EPAG - ROMI	Δ EPAG - W&R
Efficacy							
Overall response	74.6% (47/63)	71.4% (30/42)	72.3%	20.7% (6/29)	1.13 (0.21, 5.96)	2.3%	53.9%
Severe bleeding (WHO 3–5)	0.8% (0/63 – Cochrane adjustment to 0.5/63)	11.9% (5/42)	NA	10.3% (3/29)	0.03 (0.00, 1.15)	–22.1%	–9.6%
Moderate bleeding only (WHO 2)	36.5% (23/63)	71.4% (30/42)	52.2%	44.8% (13/29)	0.53 (0.12, 2.23)	–15.7%	–8.3%
Use of rescue medication	19.0% (12/63)	40.5% (17/42)	20.9%	24.1% (7/29)	0.89 (0.20, 4.02)	–1.9%	–5.1%
Mortality (derived from severe bleeding)	0.03%	NA	0.82%	0.37%	NA	0.79%	0.34%
Costs (\$)	NA	NA	NA	NA	NA	NA	NA
Drug costs	62,202	NA	84,396	22,024	NA	–22,194	40,178
Administration costs	0	NA	1,955	889	NA	–1,955	–889
Routine care costs	486	NA	486	486	NA	0	0
Rescue medication costs	983	NA	569	2,184	NA	414	–1,201
Cost of severe bleeding (G3–5)	354	NA	10,191	4,613	NA	–9,837	–4,259
Cost of moderate bleeding (G2)	802	NA	1,147	984	NA	–345	–183
Adverse events costs	1,709	NA	1,860	1,335	NA	–151	373
Mortality costs	16	NA	453	205	NA	–437	–189
Total costs	66,550	NA	101,056	32,720	NA	–34,506	33,830

Abbreviations: EPAG, eltrombopag; ROMI, romiplostim; ITC, indirect treatment comparison; NA, not applicable; W&R, watch-and-rescue.

Additionally, platelet response was assessed as a secondary endpoint. After ITC, EPAG again showed a benefit over the comparators, with incremental benefits of 2.3% and 53.9% over ROMI and W&R, respectively.

Incremental cost-effectiveness ratios (ICER) were derived to further explore cost per event (presented in Table 4). When assessing cost per bleeding event avoided, EPAG dominated ROMI for both severe and all grade bleeding events with ICERs of US\$354,197 and US\$189,303, respectively, when compared to W&R. Regarding cost per responder, EPAG dominated ROMI and had an ICER of US\$62,749 when compared with W&R. Additionally, exploratory analyses were performed using the raw (non-adjusted) data in the model (presented in the Supplementary material), which generated results consistent with the base case findings.

Probabilistic sensitivity analysis

Uncertainty in these results was assessed via PSA, in which probabilistic distributions were directly applied to the base case model. The parameters explored in the PSA are presented in Table 5.

The results of the PSA were relatively consistent with base case findings (Table 5 and Figure 2). ICERs of 99.2% and 0.8% vs ROMI and W&R, respectively, were under a

Table 4 Incremental cost-effectiveness ratios for severe bleeding events avoided

Endpoint	ICER	
	EPAG/ROMI	EPAG/W&R
Incremental cost per responder	Dominant	US\$62,749
Incremental cost per severe bleeding event avoided (WHO 3–5)	Dominant	US\$354,197
Incremental cost per bleeding event avoided (WHO 2–5)	Dominant	US\$189,303
Incremental cost per patient	Dominant	US\$62,749

Note: All costs are listed in USD.

Abbreviations: ICER, incremental cost-effectiveness ratio; EPAG, eltrombopag; ROMI, romiplostim; W&R, watch-and-rescue.

Table 5 Probabilistic sensitivity analysis results – ICERs for cost per severe bleeding avoided

	EPAG/ROMI	EPAG/W&R
Mean	– 169,568	526,907
Proportion below threshold (\$)		
25,000	97.5%	0.3%
50,000	98.3%	0.5%
100,000	99.2%	0.8%
150,000	99.6%	1.5%
250,000	99.9%	14.6%
500,000	100.0%	79.8%
1,000,000	100.0%	98.8%
10,000,000	100.0%	99.7%

Note: All costs are listed in USD.

Abbreviations: ICER, incremental cost-effectiveness ratio; EPAG, eltrombopag; ROMI, romiplostim; W&R, watch-and-rescue.

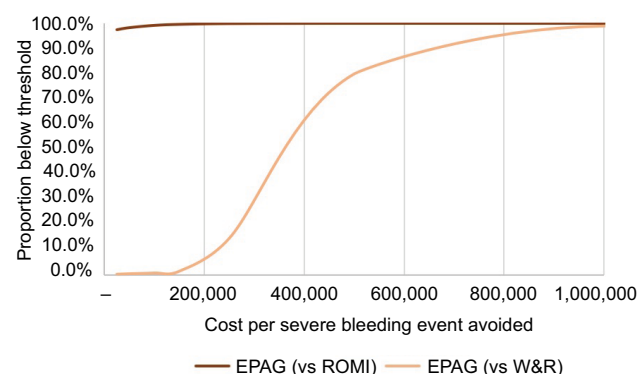


Figure 2 Cost-effectiveness acceptability curve (per severe bleeding event avoided).

Note: All costs are listed in USD.

Abbreviations: EPAG, eltrombopag; ROMI, romiplostim; W&R, watch-and-rescue.

cost-effectiveness threshold of US\$100,000, while 99.6% and 1.5% were under a cost-effectiveness threshold of US\$150,000.

Deterministic sensitivity analyses were also intended to assess incremental cost-effectiveness for severe bleeding. However, these analyses were not feasible because EPAG was dominant over ROMI for severe bleeding and therefore the relevant base case ICER was unavailable.

Discussion

In our model, TPO-R agonists were assessed for the treatment of pediatric patients with chronic ITP after comparing two robust randomized clinical trials. EPAG showed favorable rates in all endpoints assessed compared to both ROMI and W&R. EPAG-treated patients had fewer severe bleeding events than ROMI and W&R (0.8% vs 22.9% vs 10.3%, respectively), in addition to fewer moderate bleeding events (36.5% vs 52.2% vs 44.8%, respectively) which resulted in significantly lower estimated bleeding-related costs. Additionally, EPAG showed higher platelet response rates and lower mortality relative to the comparators.

EPAG, ROMI, and W&R had total estimated costs of US\$66,550, US\$101,056, and US\$32,720, respectively, with drug costs comprising most of the price for all comparators. The lower total cost of EPAG and improved outcomes led EPAG to dominate ROMI in all endpoints assessed. When compared to W&R in our assessment, EPAG had a higher total cost but had improved outcomes. Comparing EPAG to W&R yielded ICERs of US\$354,197 per severe bleeding event avoided, US\$189,303 per any grade bleeding event avoided, and US\$62,749 per platelet response. Probabilistic sensitivity analysis results were relatively consistent with the base case findings.

This analysis, while robust, is accompanied by some minor limitations. Trial endpoint definitions sometimes varied in the literature, direct matching and data selection were therefore challenging. Rituximab and splenectomy, two common treat-

ments for cITP, could not be included as comparators due to a lack of available data. The time horizon used in this model was relatively short but allowed modeling of within-trial endpoints without the need for extrapolation techniques.

We present the most comprehensive CCM to date comparing EPAG, ROMI, and W&R in children with cITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. This data is of interest to physicians and healthcare decision-makers who wish to determine the best available treatment options for pediatric ITP patients. The results of our analysis indicate that EPAG is cost-effective for the treatment of pediatric cITP patients in terms of cost per severe bleeding event avoided, though the results describing the costs and benefits of other outcomes are mixed.

Conclusion

Overall, EPAG was preferred over ROMI and W&R. Additional analyses incorporating long-term extrapolation and preference-based outcomes would complete the evidence base for the treatment of pediatric cITP.

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Author contributions

GT and MD made substantial contributions to the conception and design of this study and also analyzed and interpreted data. MB, QS, BE, AR and AB contributed to conception and development of the analysis and evaluation and interpretation of the data. All authors contributed by drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

GT and MD are employees of Purple Squirrel Economics. MB, QS, AR, and BE are employees of Novartis Pharmaceuticals. The authors report no other conflicts of interest in this work.

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